position for the species from where the FR is derived.

10. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4, 5, 6, 7, 8, [and] or 9, which specifically binds to an antigen with an affinity of between 10^{7} M^{-1} and 10^{11} M^{-1}.

11. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4, 5, 6, 7, 8, [and] or 9, which specifically binds to an antigen with an affinity of between 10^{8} M^{1} and 10^{10} M^{-1}.

A3

12. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4, 5, 6, 7, 8, [and] or 9 which is substantially pure.

13. (Amended) A pharmaceutical composition comprising a re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4, 5, 6, 7, 8, [and] or 9 in a pharmaceutically acceptable carrier.

REMARKS

Claims 1-24 are pending in this application. Claims 14, 15 and 20-24 were withdrawn from consideration by the Examiner to whom this application has been assigned. By this Amendment, applicant has amend claims 2 and 4-13. Applicant maintains that the Amended claims are well supported by the specification filed and there is no issue of new matters. Accordingly, applicant respectfully requests the entry of this Amendment.

Specification

The Examiner has objected to the disclosure of this application. Accordingly, without conceding to the correctness of the Examiner's position and to expedite the prosecution of this application, Applicant has hereinabove amended the specification for a new Abstract. Applicant believes that the new Abstract should obviate this ground of objection.

Claim Objections

The Examiner objected to Claims 2, 4, 5 and 6-13 because of the some informalities. Accordingly, without conceding to the correctness of the Examiner's position and to expedite the prosecution of this application, Applicant has hereinabove amended Claims 2 and 4-13. Applicant believes that the amended claims 2, and 4-13 should obviate this ground of objection.

112 Second Paragraph rejections

The Examiner rejected Claims 1-3 under 35 USC 112, second paragraph.

In response, regarding a, line 2 of claim 1: "immunoglobulin containing the heavy and/or light chain" means it does not require both chains to be FR-patched, either one of the heavy or light chain, or both can be FR-patched. In line 6 of claim 1: "heavy and light chain" refers to FRs from heavy chain will be patched to replace the corresponding FRs of heavy chain, and FRs from light chain patched to replace the corresponding FRs of light chain.

For b, the "affinity comparable to" shall mean within 10-fold of.

For c, the "said re-engineered immunoglobulin chain" refers to an immunoglobulin chain re-engineered according to the method of framework-patching, or a re-engineered immunoglobulin qualified to be called framework-patched as recited in the preamble.

For d, "different immunoglobin chain" is just recited a few words before as "at least two different sources of immunoglobulin chains".

For e, Claims 2-5, "positions known to be close to" refer to both linear and tertiary senses for an ordinary skilled artisan.

For f, the amino acids listed in claim 4 are EXAMPLES of conservative pairs of amino acids. Those separated by a comma (,) are conservatively similar amino acids, and different groups of conservatively similar amino acids are separated by a semi-colon (;).

For g. applicant maintain that it is well published in the field of biochemistry and clearly understood what the meaning of conservatively similar amino acids is. Therefore, the claim should not be considered as indefinite.

For h, "preferably 100%" means that it is identical.

Finally, for I, the "back mutated amino acids" refers to "re-introduced amino acids from the parent immunoglobulin framework outside". The meaning of the back mutated amino acids is therefore clearly defined. In short, they refer to those framework amino acids from the parent antibody being re-introduced back to the corresponding framework positions in the FR-patched antibody.

Accordingly, in view of the foregoing, applicant respectfully request the reconsideration and withdrawal of this ground of rejection.

112 First Paragraph Rejection

In response, Applicant respectfully traverses this ground of rejection for Claims 16-19.

Biological Deposits

Applicant maintains that a person skilled in the art of antibody engineering can follow exactly what is described in the specification to design the framework patched sequence from a murine antibody (or antibody from different species). The specifications are clear and easy to follow, and provide a step-by-step instructions on the selection of each compartmentalized frameworks for patching, and give sufficient criteria based upon which residue replacements and modifications can be introduced. These instructions/criteria will allow one skilled in the art to design the proper amino acid sequence for the framework patched antibodies.

The conversion from amino acid sequence to DNA sequence requires only text book knowledge, and can be aided by a variety of DNA software, such as McVector, or using the GCG system. With the availability of the DNA gene sequence, one can gene-synthesize the V regions of either original murine antibody, or the framework-patched antibody, another routine procedure for any laboratory with molecular biology activities, and use these synthetic gene sequences to put into known antibody cassettes and finally expression vectors containing promoter, and the respective heavy and light chain constant region sequences. The methods of cloning synthetic or PCR amplified V region sequences into expression vectors are widely available in different university research laboratories, and industry (For example, Leung et al. 1994. Chimerization of LL2, a rapidly internalizing antibody specific for B cell lymphoma. Hybridoma 13:469; Verhoeyen et al. 1988. Reshaping human antibodies: grafting an antilysozyme activity. Science 239:1534). Expression of the re-engineered antibody can be done in most molecular biology laboratories by electroporation (Leung et al. 1994. Chimerization of LL2, a rapidly internalizing antibody specific for B cell lymphoma.

Hybridoma 13:469; Co et al. 1992. Chimeric and humanized antibodies with specificity for the CD33 antigen. J Immunol. 148:1149).

Except the way based on which the amino acid sequence for the framework patched antibody is designed (the essence of the present invention) is drastically different in principle and concept from all known humanization procedures, the assembly of the designed gene sequence, construction of expression vectors, and the final expression of the recombinant protein, their purification and analyses etc., are basically the same as in the construction of any chimeric or humanized antibody, and those who are skilled in the art will find implementation of the present invention requires only routine procedures. Therefore, it would NOT require undue experimentation to reproduce the claimed antibody species hpRFB4 and hp1F5.

Both murine RFB4 and 1F5 are commercially available, and can be used to evaluate and compare the biological activities with the engineered antibodies, be them chimeric or framework-patched. The biological activities of the FR-patched antibodies and the validity of method described in the present invention can therefore be readily evaluated.

Since the sequences of the FR-patched antibodies are described in the present invention, a person skilled in the art of antibody engineering can assemble the sequences according to the present invention, construct expression vectors, and evaluate the activities of the antibodies within reasonable time frame. Therefore, the biological materials are readily available, reproducible and assessable by persons skilled in the art.

Undue experimentations

In response to the rejection based on the arguments on p.10-p.11 of the Office Action, Applicant would like to point out that there might be a misunderstanding the examiner has on the claims. The examiner might have mistaken FRs as CDRs. Throughout the application, CDRs are left untouched, no mutations would be brought within the canonical CDR sequence. Therefore, there is no disagreement with the findings of Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 p.1979). There is no indication that the FR-patched immunoglobulins as defined by the claims "may contain less than the full complement of CDRs from the heavy and light chain variable regions in unspecified order and fused to any human or non human framework sequence" (p.11 of Office Action, lines 1-3). All FR-patched immunoglobulins will have the ORDER & SEQUENCE of CDRs left unperturbed. Nor will the heavy chain CDRs be patched with light chain FRs. Applicant would like to note that, in the application, it is always said the heavy or light chain FRs from parent immunoglobulin will be patched with the CORRESPONDING FRs from human antibodies. It is explicitly clear that, for example, the FR1 from the VH of a parent immunoglobulin will only be patched with the FR1 of a suitable human/primate VH sequence. "Corresponding" here means corresponding to the heavy and light chain type, and the segment number of the FRs.

On p. 11, the examiner rejects Claims 13 and 19 which encompass pharmaceutical compositions comprising an immunoglobulin.

Applicant would like to point out that there are two examples quoted in the application, i.e., hpRFB4 (anti-CD22) and hp1F5 (anti-CD20). there have been sufficient data supporting chimeric or humanized antibodies carrying human Fc can be used in its naked form to induce tumor regression for Non-hodgkin's

lymphoma. In the case of hp1F5, it is an anti-CD20 antibody. Similar products either in its naked form or as radioisotope conjugates have been approved by FDA for marketing in the US. They are Rituxan and Zevalin from IDEC/Genentech. The pharmaceutical composition and dosing regimen for these two products are well established. In the case of Rituxan, it is used in its naked form (i.e. not conjugated with any effector molecules) to treat NHL patients once every week for four week, i.v infusion, and each infusion of 375 mg/m^2, and kept at a pharmaceutical composition of 9 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dehydrate, 0.7 mg/ml polysorbate 80, in WFI, at a pH of 6.5. This is known to induce clinically an objective response rate of > 50%.

In the case of hpRFB4, it is an anti-CD22 antibody. A similar product in Phase III clinical trial, Epratuzamab (Lymphocide), has demonstrated clinical efficacies with an objective response rate of >60%. The product is a humanized antibody carrying a human Fc, used in its naked form, at an infusion of 300-450 mg/m^2, once a week for four weeks, using a pharmaceutical composition similar to Rituxan. However, this antibody does not show anti-tumor activities in its naked form in animal experiments. This agrees with the examiners in that "results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients".

There are numerous examples of antibodies showing efficacies in treating cancers, approved or to be approved by the FDA. Antibodies have represented a class of protein drugs with predictable safety profile, well characterized physical and chemical properties, stabilities, method of production, purification and formulation. It has been shown that when an antibody against a specific target has shown clinical efficacies, different antibodies with similar target

specificities will exhibit comparable level of clinical efficacies. There are antibodies (chimeric and humanized) against different antigens (RSV, CD33, CD147, CD20, CD22, gIIb/IIIa, TNF, CD3, etc.) showing clinical efficacies against a variety of diseases (CML, NHL, rheumatoid arthritis, chron's disease, transplantation, viral infection, etc.).

Based on the above, there are sufficient objective bases, backed up with real examples in the form of marketed anti-cancer products, and products in clinical trials, upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition effective for its intended use. In the case of the examples quoted, anyone working in the field of antibody and lymphoma treatment would have reasonably predict that a similar pharmaceutical composition as in Rituxan and Epratuzamab, and in the dose range of 200 - 400 mg/m^2, once a week for 4 weeks, should be safe, and clinical efficacious in human. There is no need to perform undue experimentation in order to practice the claimed invention, especially for the two examples of antibodies quoted.

Accordingly, in view of the foregoing, applicant respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Claims Rejections - 35 U.S.C. §102(b)

The Examiner rejected Claims 1-13 under 35 U.S.C. 102(b) as being anticipated by Queen, et al., U.S. Patent 5,693,762, issued December 1997 (*Office Action, page 13*).

In response, Applicant respectfully traverse the above ground of rejection. Applicant maintain that the claimed invention is not anticipated by Queen et al.

Queen et al (US Patent 5,693,761; US Patent 5,693,762) teach humanization by the method of CDR grafting. In the teaching of Queen et al., the framework from ONE particular human (acceptor) immunoglobulin with the highest homology to that of the parent (donor) immunoglobulin is chosen as the template, and the CDRs from the donor immunoglobulin are grafted onto the acceptor framework template. The framework Queen et al. refer to and used as a template is:

1. an integral and inseparable entity containing all FR1, FR2, FR3, and FR4, and
2. selected from ONE particular human immunoglobulin.

To summarize, Queen et al are specific in using the WHOLE SET of framework sequences (for both the heavy and light chain framework sequences) from ONE SINGLE donor antibody for CDR grafting/humanization.

Queen et al stated in US Patent 5,693,762 (issued 12/97) that:

> "*….wherein the sequence of the humanized immunoglobulin heavy chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin heavy chain variable region framework and comprises at least 70 amino acid residues identical to AN ACCEPTOR human immunoglobulin heavy chain variable region sequence* (US Patent 5,693,762, Claim 1, column 161)…." and "*…wherein the humanized immunoglobulin light chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin light chain variable region framework and comprises at least 70 amino acid residues identical to AN ACCEPTOR human immunoglobulin light chain variable region amino acid sequence* (US Patent 5,693,762, Claim 11, column 162).
>
> An immunoglobulin variable region (either heavy or light chain) comprises about 120 amino acids, of which approximately 20 to 30 amino acids are CDR sequences, and the remaining 90 to 100 framework sequences.
> It is explicitly clear that to have "*….AT LEAST 70 amino acid residues (framework residues) identical to AN ACCEPTOR human immunoglobulin....*" while fulfilling the "*….AT LEAST 65% framework identical to the sequence of the donor immunoglobulin…*" requirement, Queen et al teach humanization of immunoglobulin chain by grafting the CDRs from the donor immunoglobulin onto the framework of A

SINGLE acceptor immunoglobulin framework that meets the above requirements and other criteria.

In theory and principle, Queen et al are trying to make the variable regions of a humanized antibody to look like one of the known human antibodies in available databases (such as the Kabat Database) in its entirety. Queen et al attempt to make the murine antibody look as similar as possible in appearance to a human antibody in order to reduce potential immunogenicity. Not much consideration, however, from the perspective of the mechanism of immunological action resulting in such immunogenicity is taken into conjuring up the invention. In order to maintain the affinity of the humanized antibody, Queen et al assert the need to re-introduce murine (donor) framework residues back (back mutation) to the acceptor framework sequences (back mutation) at specific locations. A set of criteria is then given as the guidelines to aid identifying critical framework residues to be back-mutated (US Patent 5,693,761, Claims 10, 11, 28, 29, 30, and 37, for example).

One purpose of the present invention aims at reducing the potential immunogenicity of non-human antibodies. The method of framework-patching does not necessarily result in a humanized antibody, but a re-engineered antibody with reduced immunogenicity. Below summarizes the principles underlying the invention which are different from what Queen et al have relied on, which are:

(1) <u>the availability of a suitable framework from one single human antibody in existing antibody database</u> - this will impose inflexibility in the choice of suitable frameworks that meet the minimal criteria to be used as the templates onto which CDRs are grafted. The present invention aims to reduce immunogenicity, or increase the "human-ness", of an antibody

using an approach different from that of Queen et al. Framework as referred to in the present invention, is not viewed as one inseparable entity, nor is it confined to a single source (i.e. from one single acceptor antibody), rather, it represents any one of the four FR segments. The present invention aims to reduce immunogenicity, or increase the "human-ness" of an antibody, by first compartmentalizing the framework into four linear FR segments, namely, FR1, FR2, FR3, and FR4, and treating them separately and independently. Our goal is to find stretches of any one of these FRs that meet the criteria set forth in Claims 2 to 5 of the present invention. The choice of each individual FR, unlike the teaching of Queen et al, is not confined to one single antibody (for example, different segments of FRs can be derived from the corresponding FRs of different human immunoglobulin such as FR1 from JOH, FR2 from Vd'CL, FR3 from WES, and FR4 from RZ, as in the case of the FR-patched VK of RFB4 quoted in the application), nor is it confined to immunoglobulins of one single species (an assortment of FRs from human and other primates is allowed). And one FR after another, the selected FRs from the human or primate immunoglobulin databases will be "patched" onto the parent immunoglobulin. It is conceivable that when taken into its entirety, it is less likely that a framework referred to by Queen et al (inclusive of FR1, FR2, FR3 and FR4) from a single antibody that satisfies the criteria set forth in the present invention (and those of Queen et al) and doesn't need further modifications can be identified and used directly for CDR-grafting.

The FR-patching method provides a flexible way of dealing with the problem. First, by compartmentalizing the framework into 4 stretches, and dealing with each compartment separately and independently, the chances of finding a suitable linear

sequence from the database have drastically increased. For example, it is substantially easier to find a FR1 that fulfills the criteria as in claims 2, 3, 4 and 5, than to identify a framework from a single antibody with all FR1, FR2, FR3 and FR4 fulfilling these criteria.

The teachings of Queen et al will not suggest or make obvious to those skilled in the art to partition frameworks into independent segments, which are then dealt with separately; or to assort FRs from different sources into forming a single re-engineered immunoglobulin. To conjure up with the invention, one would have to think differently from Queen et al, and look into the matter with a perspective backed up by basic immunological considerations.

(2) the need to re-introduce onto the human (acceptor) framework template with murine (donor) amino acids from the parent antibody in order to preserve affinity - as mentioned above, when the choice of framework is confined to a single source from a single antibody, it would be difficult to identify acceptor frameworks as described by Queen et al for CDR-grafting without the need to re-introduce murine (donor) amino acids back to the human (acceptor) framework in order to maintain the affinity of the humanized antibody. In fact, most humanized antibodies reported so far contain multiple murine amino acids in their human frameworks. The inserted murine amino acids buried in a human environment can potentially create new and highly immunogenic B-cell and, most importantly, linear T-cell epitopes. It has been shown that, linear T-cell epitopes are the major contributing factors for the induction of high immunogenicity (the T-cell epitopes are presented as linear peptides in the context of MHCI/II by the Antigen Presenting Cells). Elimination of these T-cell epitopes while leaving the B-cell epitopes unperturbed by a process called "peptide threading" was shown to be sufficient

in mitigating the immunogenicity of an apparently foreign looking protein. It is therefore more important to maintain the "human-ness" of the linear segment of FR and avoid the presence of murine amino acid within that particular segment of FR in order to minimize the emergence of new T-cell epitopes, rather than to maintain the overall human appearance of the whole framework while running the risks of forming new B- and T-cell epitopes by the inserted murine amino acids.

Queen et al. fail to foresee these problems, and advocate to replacing human with murine amino acids within the human framework template in order to minimize the loss of affinity as a result of the humanization process. Queen et al also teach a set of criteria to identify the positions within the human framework that should be replaced by murine amino acids (US Patent 5,693,761 Claims 10, 11, 28, 29, 30, 31 and 37). The process is referred to as back mutation.

It is conceivable that back mutations as proposed by Queen et al should be avoided, or at least kept to a bare minimum. By patching and assorting FRs separately and independently from different antibody sources, we increase the likelihood of identifying highly homologous human FRs, and have the flexibility of finding human or primate FRs that have identical or conservatively similar amino acids to the parent antibody at positions determined to be important for affinity. The idea is to maintain the "human-ness" of the selected FRs without the need for back mutation (or such back mutation kept to a bare minimum). The method of Queen et al uses the whole framework for CDR-grafting, and it will be less likely, compared to the method of Framework-patching, that a whole framework with all critical positions for affinity identical to that of the murine immunoglobulin can be identified. One has to, therefore, follow the criteria set forth by Queen et

al and identify framework residues to be back mutated. In the present invention, a set of criteria are presented for choosing FRs so that back mutation can be AVOIDED or KEPT TO A BARE MINIMUM. The approach of Queen et al. (use whole framework, devise criteria to identify important murine amino acids for re-introduction to the human framework, a HUMANIZATION method), and the method of framework-patching (use different FRs from different sources, choose FRs separately and independently, devise criteria to identify FRs to AVOID or MINIMIZE the introduction of murine amino acids to the human FRs, a method to REDUCE immunogenicity) are drastically different, both in practice and in principle.

It should be noted that there were incidences/examples when Queen's approach is taken, scientists failed to produce humanized antibody with conserved affinity. And in these cases, the best available options would be to use chimeric antibodies. The current invention not only addresses the deficiencies of Queen et al. by minimizing the chances of introducing immunogenic T-cell and B-cell epitopes, but also gives additional flexibility in allowing the mixing and matching of FR's from different species in the construction of a re-engineered immunoglobulin of reduced immunogenicity (for example, FR1, and FR3 from human, FR2 from Primate, FR4 from parent antibody); the enhanced "human-ness" of each FR will reduce the chances of producing immunogenic peptide(s) for T-cell epitope from that segment of FR; the more FRs being replaced by corresponding human/primate FRs, even in the presence of remaining murine (or parent) FRs, the re-engineered immunoglobulin will theoretically and potentially be less immunogenic than its murine or chimeric counterpart.

In response to p.14 of this Office Action, Queen et al teach humanized antibodies wherein the framework regions are from humans and the donor are from another species.

The "donor from another species" as referred to by the teaching of Queen et al will contribute to the humanization process by "donating" the CDRs, but not the FRs. As explained earlier, Queen et al teach the use of acceptor framework from one single antibody from one single species. The present invention teaches the use of freely assorted FRs from different sources (different antibodies and different species). A significant difference between the two approaches.

p.14., this Office Action, the Examiner stated that Queen et al teach several criteria for humanization and those are that the acceptor FR is highly homologous, 60-70% to the donor (see column 2, lines 45-55):

Again, Queen et al teach humanization by first choosing an acceptor framework that is highly homologous to the donor, and the framework they refer to is derived from one single immunoglobulin, as explained earlier. The homology is for the whole framework taken in one piece or in its entirety. Whereas the present invention teaches several criteria for identifying compartmentalized FRs, which are taken separately and independently, with high level of individual homologies.

The present invention has a major advantage over the method of Queen et al. For example, an acceptor framework from a single antibody having 60-70% overall sequence homology to the donor sequence might have 50, 60, 30 and 100% sequence homologies to the corresponding FR1, FR2, FR3 and FR4, respectively; it is difficult to source from one single acceptor framework with sequence homology evenly spread among the four FRs. Therefore, as in most cases of humanization, additional murine amino acids will have to be re-introduced back to the acceptor framework, thereby increasing the chances of emergence of immunogenic epitopes, and defeating the purpose of humanization (i.e., reducing potential immunogenicity). The

present invention is designed just to avoid or minimize this problem.

p. 14, this Office Action, the Examiner stated that the human FR residue will be one or more residues that are immediately adjacent to the CDRs, or at 4-6Å from the CDR (see column 3, 14, lines 25-60)

By that, Queen et al. refer to the identification of MURINE RESIDUES/AMINO ACIDS (donor amino acids) that will have to be BACK-MUTATED/RE-INTRODUCED BACK to the human (acceptor) framework. In the quoted paragraph, Queen et al teach if one finds in the human framework chosen for CDR-grafting to have FR residues immediately adjacent to the CDRs to be DIFFERENT from that of the parent, donor immunoglobulin, or when the human framework residues, either determined by x-ray crystallography or computer modeling, to be close (at 4-6 Å) to the CDRs, to be DIFFERENT from the corresponding residues in the parent, murine immunoglobulin, then, one should BACK MUTATE, or RE-INTRODUCE the original murine (donor) residues back to the human (acceptor) framework.

The present invention teaches by a set of criteria to AVOID or MITIGATE the need to BACK MUTATE murine framework residues to the chosen FRs for patching. This is in contrary to what Queen et al propose to do.

The present invention teaches that by allowing a free-assortment of FRs from different antibodies [either from the same species (e.g. human), or a different species (e.g. primates or murine)](Claim 1), one would prefer choosing FRs with residues at positions immediately adjacent to the CDRs (Claims 2-5), or determined at 4-6Å from the CDR that are IDENTICAL to that of the parent framework, so that we DO NOT NEED TO INTRODUCE MURINE RESIDUES (OR AT LEAST NOT AS MANY) INTO THESE POSITIONS in order to maintain affinity.

To summarize: Queen et al. lay out a set of criteria and teach how to use these criteria to identify murine (donor) framework residues to be MUTATED BACK to the human (acceptor) framework template, whereas in the present invention, Leung lays out a set of criteria and teaches how to use these criteria to identify segments of frameworks (FRs) from human and other species so that one DOES NOT NEED TO introduce murine framework residues to the patching FRs, a drastically different approach attempting to achieve a goal that is in the opposite direction from that taught by Queen et al.

However, within the context of Claims 1-5, one could still find for some antibodies, even though one identifies individual FRs with the best homology to the corresponding parent FRs, and FRs with sequences immediately adjacent to the CDRs as identical or similar as possible, etc., there are still needs to BACK-MUTATE murine residues at odd locations in order to improve affinity of the FR-patched antibody. Therefore, in Claims 6-9, criteria for BACK-MUTATING parent FR amino acids to the FR-patched sequence are proposed. Although Queen et al. teach criteria for BACK-MUTATING murine amino acids into the humanized immunoglobulin, they were done onto a whole framework in a "humanization" approach. No other alternative ways are suggested, implied or otherwise, that will allow minimizing the number of murine amino acids required for back mutation. In the present invention, Claims 6-9 are built on FR-patched sequences, and the criteria used for selecting the different FRs will minimize, if not eliminate, the number of murine amino acids required to be back mutated to the FR-patched sequences, thereby reducing the number of potential B- and T-cell epitopes generated as well as the potential immunogenicity of the resultant antibody. This is a substantial improvement over the approach taught by Queen et al.

p.14. or at a position that is rare for the donor relative to the human sequence (see column 3, lines 20-26), and the affinity is $10^6 M^{-1}$ or higher and may be within 2 fold of the parent antibody (see column 3, lines 35-42), and the FR can have conservative substitutions (see column 12, lines 20-26), and the antibody comprises amino acids re-introduced from the donor (see column 12, lines 39-44), and the antibodies are substantially pure and compositions comprising such. Queen et al also teach the importance of residues immediately adjacent to a CDR or those residues that interact with a CDR which are important for affinity and computer programs to create such models of antibodies (see column 15, lines 60).

The question is addressed using reasoning and rational of the above. In short, Queen et al. lay out a set of criteria (including the above: or at a position that is rare for the donor relative to the human sequence; and the FR can have conservative substitutions; and the antibody comprises amino acids re-introduced from the donor; Queen et al also teach the importance of residues immediately adjacent to a CDR or those residues that interact with a CDR which are important for affinity and computer programs to create such models of antibodies) to help identify murine (donor) framework residues to be MUTATED BACK to the human (acceptor) framework template, whereas the present invention teaches the use of a set of criteria to help identify FRs for patching so that there are NO or REDUCED NEEDS to introduce parent FR amino acids to the FR-patched immunoglobulin (Claims 1-5). Although within the context of the current invention, a FR-patched immunoglobulin (whose needs for back mutation should have been eliminated or minimized) a set of criteria to identify parent FR amino acids that can be back mutated to the FR-patched immunoglobulin is also allowed (Claims 6-9).

Accordingly, in view of the foregoing, applicant respectfully request the reconsideration and withdrawal of this ground of rejection.

Applicants : LEUNG, Shui-on
U.S. Serial No.: 09/892,613
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Page : 24

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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